Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials

Christa Mitterbauer, Christoph Schwarz, Martin Haas and Rainer Oberbauer

Department of Internal Medicine III, Division of Nephrology, Medical University Vienna, Vienna, Austria

Abstract

Background. Bone loss remains a serious problem after kidney transplantation and is most pronounced during the first months after engraftment. Bisphosphonates are frequently used to treat post-transplant osteodystrophy, but data of large randomized controlled trials (RCTs) are missing.

Methods. We, therefore, conducted this systematic review of the literature, searching electronic databases, reference lists and abstracts from scientific meetings to identify RCTs in all languages. The primary outcome assessed was the change in bone mineral density (BMD) during the early post-transplantation period. Based on the mean BMD change presented in the identified publications, the authors were asked for the individual BMD results of all randomized patients, determined at lumbar spine and femoral neck before and after bisphosphonate therapy. Data were pooled for summary estimates by using weighted mean differences of absolute change in BMD. An analysis of covariance was performed, adjusted for individual baseline values, treatment arm and individual trial.

Results. Five studies involving 180 participants were included in our meta-analysis. Treatment with bisphosphonates showed a substantial effect in preventing post-transplant osteodystrophy. BMD decline at the lumbar spine within 6–12 months after transplantation was significantly reduced by 0.06 g/cm² in patients treated with bisphosphonates (95% CI 0.05–0.08 g/cm²). At the femoral neck, the loss of BMD was reduced by 0.05 g/cm² during this period (95% CI 0.0–0.11 g/cm²), reaching just non-statistical significance. This benefit of bone loss prevention could be reached without major side effects.

Conclusion. Bisphosphonates are effective in preventing bone loss in the early post-transplant period.

Keywords: bisphosphonates; bone loss; bone mineral density; kidney; meta-analysis; renal osteopathy; transplantation

Introduction

Bone mineral density (BMD) loss remains a serious problem after renal transplantation and is most pronounced during the first months after engraftment. Julian and colleagues [1] reported a mean BMD decline at the lumbar spine of 6.8 and 8.8%, respectively, 6 and 18 months after successful renal transplantation. Consequently, the risk for fractures is clearly increased in this population [2,3]. The reasons for augmented bone loss are manifold, but corticosteroid therapy has been shown to be a major contributor, considering the fact that steroid doses used for maintenance immunosuppression and to treat acute rejections are the highest during this period [4]. Additionally, calcineurin inhibitors, persistent hyperparathyroidism as well as post-transplant tubular impairment of calcium and phosphorus reabsorption may contribute to the rapid loss of bone mass. These factors add up to the pre-existing causes of renal osteodystrophy, such as secondary hyperparathyroidism, parathyroid hormone resistance of bone cells, disorders in vitamin D metabolism, hypogonadism, amyloidosis, diabetes mellitus, patient immobility or aluminium toxicity [5,6]. Furthermore, the immunosuppressive treatment of the primary renal disease and the long-term use of loop diuretics contribute to the bone loss [7].

In view of the high prevalence of abnormal BMD and fractures in kidney transplant recipients, several studies were carried out to evaluate the efficacy of anti-osteoporotic drugs given in the immediate post-transplant phase. In the last few years, bisphosphonates were increasingly used to treat renal osteodystrophy. However, good evidence for a reduced risk of bone loss and fractures exists only for post-menopausal women with osteoporosis, steroid-induced osteoporosis in the
general population and patients with neoplastic bone disease [8–10]. The number of controlled clinical trials in renal transplant recipients is limited and the magnitude of effect varies considerably across the studies. Therefore, tools such as meta-analysis can be applied to pool results, providing a more precise estimate of the effect. The present meta-analysis aims to systematically summarize the effects of bisphosphonate treatment on bone loss within the first year after kidney transplantation.

Methods

Literature search

We searched MEDLINE database (1966–December 2004), EMBASE database (1989–December 2004) and the Cochrane Controlled Trials Register in the Cochrane library to identify all clinical trials relating to the use of bisphosphonates after renal transplantation. Keywords used in electronic database search included ‘renal’ or ‘kidney transplantation’ combined with ‘bisphosphonates’ or the generic name of various bisphosphonates such as alendronate, pamidronate, ibandronate, zoledronate, etidronate, risedronate and clodronate. The reference lists of all studies included in the meta-analysis were examined for other relevant articles missed by the electronic searches. Abstracts from scientific meetings of the last few years were manually searched and selected if sufficient information was available in the body of the abstract, including but not limited to the American Society of Nephrology, the International Transplant Society and the European Dialysis and Transplantation Association. Authors of included reports and experts in kidney transplantation were contacted to locate unpublished studies.

Study selection

We included randomized controlled trials (RCTs) which investigated the use of bisphosphonates in renal transplant recipients, alone or in combination with calcium and/or vitamin D, with a control group receiving no treatment or placebo, alone or in combination with calcium and/or vitamin D. We chose studies in which participants were men and/or women over the age of 18, receiving their first or subsequent cadaveric or living renal allograft. Trials in any language without any restriction in sample size, in which a bisphosphonate in any dosage was used, were eligible. Due to the shortgage of bisphosphonate studies on long-term kidney transplant recipients and the heterogeneity of these mostly small reports concerning study population and bisphosphonate administration, we decided to focus our meta-analysis on trials investigating the effect of bisphosphonates in the quite homogeneous group of de novo renal transplant recipients. This decision was supported by the fact that the most severe loss of BMD occurs within the first months after organ transplantation, the phase where corticosteroid doses administered for maintenance immunosuppression and to treat acute rejections are the highest.

Outcome measure and data extraction

The primary outcome assessed and required for inclusion in the meta-analysis was the change in BMD within the first year after successful kidney transplantation. Data regarding the number of new fractures and side effects were collected if present.

Based on the mean change of BMD presented in the identified publications, we contacted the authors and asked for the individual bone densitometry results, expressed in gram per square centimetre, of all randomized patients, determined at lumbar spine and femoral neck at baseline and after bisphosphonate treatment. From these data, the individual absolute changes in BMD during study period were calculated, leading to an optimal comparability of all available studies regarding BMD changes within the first year after transplantation.

Study quality

The quality of trial reports was assessed without blinding to journal or authorship using the guidelines of Jadad et al. [11]. The quality items assessed were random allocation, blinding status of participants and investigators as well as the completeness of follow-up. The possible score ranged from zero to five, with five indicating the best quality.

Data analysis

Statistical analyses were conducted separately for BMD alterations at the femoral neck and the lumbar spine, determined within the first year after successful renal transplantation. If 6 and 12 months’ BMD results were available, the 12 months’ data were used for the calculation of the individual BMD changes during study period. Data were pooled for summary estimates by using fixed and random effects models [12,13]. Heterogeneity of the trials was assessed using a chi-square test, with P-values of <0.05 to denote statistical significance. A fixed effects model was applied initially. Where a significant heterogeneity existed, a random effects model was included in the analysis. The continuous outcome results were expressed as weighted mean differences (WMDs) and their 95% confidence intervals (CI). Forest plots were used for graphical representation of the results.

A multivariable linear regression analysis of covariance (ANCOVA) using follow-up scores as dependent variable was performed with the individual BMD data adjusted for baseline BMD, treatment arm and study site [14]. This regression method takes into account that the absolute baseline values are negatively correlated with the change during the study period, because patients with low scores at baseline generally improve more than those with high scores. Furthermore, sequential measurements tend to show a regression towards the mean. We illustrated the treatment effect by showing the regression lines of pre- and post-treatment scores of both groups. The vertical distance between the two regression lines corresponds to the estimated difference between the control and bisphosphonate arm.

Statistical analyses were conducted with SAS 9.1 (Cary, NC, USA) statistical software.

Results

Literature search

Electronical literature search with the afore-mentioned keywords identified 330 potentially relevant abstracts.
From these and from reports found by manual search, a total of 17 studies were ultimately selected for full-text review. Nine of these were rejected because they did not fulfill the inclusion criteria, leaving a total of eight independent trials. As described above, the authors of these detected studies were asked for the individual bone densitometry results of all randomized patients, determined before and after bisphosphonate therapy. In consequence, two trials, which were available in abstract form only, had to be excluded due to the incompleteness of the actually available BMD measurements. Another small study could not be taken into account because the authors did not provide the individual BMD results despite six requests [15].

Altogether, five studies with 180 participants were identified, which examined the treatment of renal osteopathy with bisphosphonates in the early post-transplant period and made the requested BMD data available [16–20]. A flow chart indicating the identification of RCTs for inclusion in the meta-analysis is depicted in Figure 1.

**Included trials**

Table 1 shows the characteristics of all trials included in the meta-analysis. Three studies used the bisphosphonate pamidronate [16,17,20], one trial used zoledronate [19] and one ibandronate [18]. Apart from Kovac and colleagues [20], who administered daily oral pamidronate, the other investigators applied intravenous bisphosphonates in a cyclic fashion. Additionally, all included patients received daily calcium, with one investigator permitting supplementation with dairy products [18]; vitamin D was administered in three of five studies [16,17,20].

At the time of kidney transplantation, the median iPTH levels ranged between 200 and 417 pg/ml in the five analysed studies. With the exception of Haas et al [19], there was no significant difference in iPTH serum concentrations between the bisphosphonate and control group.

All reports used dual energy X-ray absorptiometry to determine BMD. Data on bone loss at the lumbar spine (L1 or L2–L4) were reported in all five detected trials. Only four studies measured BMD changes at the hip, three of them at the femoral neck. The report from Coco et al [16] did not further specify the investigated hip region. Besides the baseline BMD determination at the time of engraftment, two authors provided 6 months' data to calculate the individual changes in BMD [19,20]; with two other trials the calculations could be done with BMD results evaluated 12 months' after transplantation [17,18]. Partly 6 and partly 12 months data were provided by Coco et al [16]—whenever

---

**Fig. 1.** Identification of RCTs for inclusion in the meta-analysis.
available, the 12 months’ data were used for the calculations.

Analysis of lumbar spine and femoral neck BMD

Data were analysed separately for BMD alterations at the femoral neck and the lumbar spine. BMD decline at the lumbar spine within 6–12 months after transplantation was significantly reduced by 0.06 g/cm² in patients treated with bisphosphonates (WMD 0.06 g/cm²; 95% CI 0.05–0.08 g/cm²; \( P < 0.001 \)). The test for heterogeneity indicated that the individual studies were relatively homogeneous (\( P = 0.47 \)). Thus, the fixed effects model showed virtually identical estimates as the random effects model, and only the fixed effects model results are displayed in Figure 2.

The ANCOVA revealed an estimated BMD difference of 0.059 g/cm² between control and treatment group (\( P < 0.001 \)) at the lumbar spine (Figure 3). The majority of variability of the post-transplant BMD could be explained by the pre-transplant BMD (\( R^2 = 0.85 \), \( P < 0.001 \)) and only a minor fraction of variability could be attributed to the bisphosphonate treatment (\( R^2 = 0.03 \), \( P < 0.001 \)). The study site revealed no significant impact on post-treatment BMD. The adjusted \( R^2 \) of the linear regression model was 0.88 (\( P < 0.001 \)) suggesting an excellent model fit.

At the femoral neck, the chi-square test revealed significant heterogeneity of the trials, implying the application of a random effects model. In patients treated with bisphosphonates, the loss of BMD was reduced by 0.05 g/cm² during the study period (WMD 0.05 g/cm²; 95% CI 0.0–0.11 g/cm²). However, using the random effects model resulted in a just non-significant WMD with a \( P \)-value of 0.067. The WMD of BMD loss at the femoral neck using the random effects model is displayed in Figure 4.

The ANCOVA showed an estimated BMD difference of 0.048 g/cm² between treated and non-treated patients (\( P < 0.001 \)) when adjusted for absolute BMD levels at baseline and trial site (Figure 5).

Bone fractures and adverse effects

Three studies reported the number of participants with new fractures during study period. Coco et al. [16] found a higher number of fractures in the control group (two vs one in the bisphosphonate group), Grotz and colleagues [18] reported two fractures in each group, and no bone fracture occurred in Kovac’s trial [20].

None of the studies noted withdrawals due to side effects. Not all adverse effects were listed in the reports, but in those that did provide information transient hypocalcaemia, bone pain and flatulence were mentioned as temporally related to bisphosphonate administration.
Graft function and immunosuppression

All five trials used calcineurin inhibitor-based immunosuppressive regimens with similar cumulative doses of glucocorticoids in treatment and control arm during study period. No trial remarked deterioration of kidney transplant function due to bisphosphonate therapy with comparable renal graft outcome at the end of the follow-up period. Grotz and colleagues [18] noticed significantly more acute graft rejections in the control group, the other investigators reported comparable numbers of rejection episodes in both groups and no data were provided in Kovac’s report [20].

Discussion

This meta-analysis was performed to evaluate the efficacy of bisphosphonates in prevention and treatment of post-transplant renal osteodystrophy. For this purpose, we analysed the results of all available RCTs, which investigated the effect of bisphosphonate therapy on BMD within the first year after successful renal transplantation. This time frame was chosen due to the observation that bone loss is highest in this early post-transplant period with subsequent decrease and, in some cases, even stabilization of bone density [21].

The ultimate study endpoint for the evaluation of osteoprotective interventions in the general population is the fracture rate. However, due to the small numbers of patients in renal transplant trials and the limited follow-up time, BMD is generally accepted as valid surrogate endpoint for interventional studies.

The pooled results of this meta-analysis demonstrate a decreased loss of BMD in those renal graft recipients...
treated with bisphosphonates in the immediate post-transplant period. At the lumbar spine, the loss of BMD was reduced by 0.06 g/cm² for bisphosphonate-treated subjects compared with the control group; at the femoral neck, BMD decline was just not significantly reduced by 0.05 g/cm² within the first 6–12 months after engraftment. This benefit could be reached without major side effects and without deterioration of kidney transplant function following bisphosphonate therapy. None of the studies noted withdrawals due to serious adverse events.

Besides the small study from Kovac and coworkers [20], the investigators used intravenous infusions of bisphosphonates, which were applied 2–4 times, first at the time of transplantation, last 1–9 months thereafter. These regimens of 2–4 parenteral doses were simple to administer, obviously well-tolerated and required minimal additional monitoring of the patients throughout the post-transplant period. Moreover, the regimens used ensured high compliance and avoided the practical difficulties of oral bisphosphonates in these complex patients receiving multiple therapies.

Although, early bisphosphonate therapy seems to be beneficial in the immediate post-transplant phase, as evaluated by our analysis, the optimal duration and dosage remains to be determined. As shown by Coco and colleagues [16], however, prolonged and more intensive treatment may increase the risk of adynamic/low turnover bone disease.

A recent systematic review of RCTs by Palmer et al. [22] analysed the efficacy of various therapies for preventing bone loss in renal transplant recipients, including bisphosphonates, vitamin D analogues and calcitonin. The treatment effects were compared with one another and with a control group receiving no bone-sparing therapy. Apart from the bisphosphonates vs control analysis, however, all other summary estimates were calculated, from the most two individual studies. Considering the small sample size of those trials, the power of these pooled analyses is limited.

Palmer and coworkers [22] primarily included all reports investigating the effect of bisphosphonates on post-transplant bone loss, not only the studies on de novo renal graft recipients. In contrast to our meta-analysis, however, the published mean BMD results were used for effect estimations. Thus, Palmer and colleagues [22] depended on sufficient data provided in the publications, which allowed them to calculate WMD. In fact, not all articles provided baseline and follow-up BMD data, particularly then, when results were not statistically significant. Additionally, the authors chose different units for expressing BMD results, such as gram per square
centimetre, z-score, r-score, or the absolute or percentage mean BMD change during follow-up, which makes it difficult to compare and pool results. Consequently, from 12 primarily identified bisphosphonates vs control studies, only seven could be used from Palmer et al. [22] for pooled risk estimates concerning bone loss at the lumbar spine and only four for summary estimates at the femoral neck—although they included reports on de novo and long-term transplant recipients. Due to this simultaneous analysis (patients between 0 and 72 months after transplantation), Palmer and coworkers [22] noticed significant heterogeneity among the trials. Bisphosphonate therapy given in the first months after transplantation, when bone loss is greatest, may have a greater impact on BMD than treatment several years after engraftment.

For our meta-analysis, in contrast, the authors of the included studies were asked for the individual bone densitometry results, expressed in gram per centimetre, of all randomized patients, determined at lumbar spine and femoral neck at baseline and after bisphosphonate treatment. From these data, the individual BMD changes during the study period were calculated for all subjects. Therefore, an optimal comparability of all available studies, regarding BMD changes within the first year after transplantation could be reached. A major advantage of the present analysis is that individual data were obtained from all trial sites and therefore an adjustment of treatment effect could be performed according to the BMD present before renal transplantation, which is the strongest predictor of bone loss after engraftment.

In summary, our integration of the available individual clinical data suggests that bisphosphonate therapy in the first months after renal transplantation may be beneficial to counterbalance the substantial bone loss occurring within the first year after engraftment. However, the potential induction of adynamic or low turnover bone disease needs to be considered in the decision of its use in each patient individually.

Acknowledgements. We are indebted to all the authors who provided the individual data of all participating study patients. This study was supported by the Austrian Science Funds and the Verein zur Förderung der nephrologischen Forschung (grant No. P-15679 to R.O.).

Conflict of interest statement. None declared.

References


Received for publication: 6.2.06
Accepted in revised form: 21.2.06